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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,626	GREEN ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

DETAILED ACTION

1. Applicant's remarks, filed 06/07/2005, are acknowledged.

Claims 1 – 26 are pending.

Claim 20 has been withdrawn from consideration as being drawn to non-statutory subject matter.

2. Applicant's election with traverse of Group XXVII (claims 17 and 26, drawn to a method of treating or preventing a disorder by administering a an antibody to polypeptide of SEQ ID NO:6) in the reply filed on 06/07/2005 is acknowledged.

No grounds for traversal have been presented.

The requirement is still deemed proper for the reasons of record, and is therefore made FINAL.

3. Claims 1 – 16, 18, 19, and 21 – 25 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions.

Claims 17 and 26, as they read on SEQ ID NO:6, are under consideration in the instant application.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the sequences disclosed at least in Figure 4 and the accompanying Brief Description of Drawings *are not accompanied by SEQ ID Numbers*. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Applicant is reminded to amend the specification and the claims accordingly.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

5. Figure 4 is objected to because the reference sequence (SEQ ID NO:6) is not identified in the Figure or in the accompanying Description (i.e. it is not clear which of the sequences in the alignment is SEQ ID NO:6).

6. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 35 U.S.C. 120 is acknowledged.

However, the provisional applications USSN 60/152,383, 60/172,909, and 60/183,578 upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for claims 17 and 26 of this application. Specifically, insufficient support was identified for the limitation of "a method of treating or preventing an immune disorder by administering an effective amount of an antibody to a polypeptide of SEQ ID NO:6."

Consequently, the claims have been accorded the priority of the filing date of the priority PCT application, i.e. 08/31/2000.

It is noted that the provisional application USSN 60/183,578 discloses the polypeptide sequence of SEQ ID NO:6 (Figure 1), and discloses that it can be useful in the generation of antibodies for use in therapeutic methods (page 3 last sentence). However, this is not seen as providing adequate support under 35 USC 112, for the instant claim language.

Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports the instant claim limitations.

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

8. It is noted that no IDS has been filed in the instant application.

9. The use of trademarks has been noted in this application (e.g. Triton on page 52). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 17 and 26 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 17 and 26 are indefinite in being dependent on non-elected claims.

It is noted that the dependent claims 17 and 26 encompass all the limitations of base claims 12 and 10.

Applicant is invited to amend the claims to incorporate the limitations of the non-elected base claims.

B. Claims 17 and 26 are indefinite in the recitations of "derivative" and "analog," because the metes and bounds of the terms are not clear. The specification discloses that "derivatives" are amino acid sequences formed from native compounds either directly of by modification or partial substitution (pages 10 – 11, bridging paragraph), and "analogs" are amino acid sequences that have structure similar to, but not identical to, the native compound but differ from it with respect to certain components or side chains (ibid.) These ambiguous "definitions" render the claims vague and indefinite, because one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

C. Claims 17 and 26 are indefinite in the recitation of "a homolog of a polypeptide," because the metes and bounds of the term are not clear. The specification discloses on page 11, lines 16 – 20, that the term "homologous amino acid sequence" refers to a sequence characterized by a homology at the amino acid level.

Homology is also described as identity of at least about 30%, 50%, 70%, 80%, or 95%, with a preferred identity of 80-95% (page 11 lines 8 – 10). These ambiguous "definitions" render the claims vague and indefinite, because one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

D. Claims 17 and 26 are indefinite in the recitation of hybridization under "stringent conditions," because the metes and bounds of the term are not defined in the claim. It is noted that examples of stringent hybridization conditions are disclosed at page 15 of the specification. Incorporating a specific set of conditions, supported by the specification, into the claims would obviate this rejection.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 17 and 26 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide a sufficient enabling description of the claimed invention.

The claims are directed to method of treating or preventing an immune response-associated disorder (or a pathological state) by administering an antibody to a polypeptide of SEQ ID NO:6. (It is noted that issues relating to scope of the claims as they read of on a plurality of antibodies to variants of SEQ ID NO:6 are addressed separately is sections 14 and 15 infra).

The polypeptide of SEQ ID NO:6 is alleged to have a variety of possible biological activities (e.g. pages 80 – 81, bridging paragraph). This allegation is presumably based on the limited sequence similarity between SEQ ID NO:6 and immune costimulatory molecules B7-1 and B7-2 (e.g. Figure 4).

However, a person of skill in the art is not enabled to practice the claimed methods, because it was well known in the art at the time the invention was made that different molecules having sequence similarity to costimulatory molecules B7-1 and B7-2 have different, and often opposite, functions (e.g. reviewed by Riley et al., 2005, Blood, 105: 13 – 21; see entire document). For example, the action of B7 molecules on T cells induces resistance to apoptosis, long term expansion, and production of high levels of IL-2 (e.g. page 14 first column), while the role of B7-related molecules PD-L1 and PD-L2 appears to be in maintaining peripheral tolerance, in part by inhibiting T cell proliferation (e.g. page 15). Therefore, it was highly unpredictable at the time the invention was made which, if any, role the polypeptide of SEQ ID NO:6 may play in the immune system, and what, if any, effect would antibodies to this polypeptide have in any immune-response associated disorder.

In the absence of sufficient guidance, or working examples, the effect of antibodies to SEQ ID NO:6 in vivo is unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

14. Claims 17 and 26 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide a sufficient enabling description of a method of treating or preventing an immune response-associated disorder (or a pathological state) by administering an antibody that selectively binds to:

(a) a polypeptide comprising an amino acid sequence of SEQ ID NO:6;

(b) a fragment of a polypeptide comprising an amino acid sequence of SEQ ID NO:6, wherein the fragment comprises at least 6 contiguous amino acids of SEQ ID NO:6;

(c) a derivative of a polypeptide comprising an amino acid sequence of SEQ ID NO:6;

(d) an analog of a polypeptide comprising an amino acid sequence of SEQ ID NO:6;

(e) a homolog of a polypeptide comprising an amino acid sequence of SEQ ID NO:6; or

(f) a naturally occurring allelic variant of a polypeptide comprising an amino acid sequence of SEQ ID NO:6, wherein the polypeptide is encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule of SEQ ID NO:6 under stringent conditions.

It is noted that method claims 17 and 26 encompass all the limitations of base claims 10 and 12.

The instant claims do not provide sufficient structural and functional characteristics of the genus of polypeptides encompassed by the instant claim

language, coupled with a known or disclosed correlation between function and structure. Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification discloses a single polypeptide of SEQ ID NO:6, and polypeptides of SEQ ID NOS: 2 and 4 which differ in the number of Ig-like domains. The instant claims encompass in their breadth *any* polypeptide at lease 80% identical to *any* fragment, derivative, analog, homolog, or allelic variant of the sequence. However, there is insufficient enabling description of the claimed genus of polypeptides in the absence of defining the relevant identifying characteristics such as the structure or other physical and/or chemical characteristics of the claimed genus.

"Percent identity."

The claims recite a genus of polypeptides having at least 80% identity to a reference sequence, but do not require that the encoded polypeptides share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed three BLAA polypeptides, and thus has disclosed only three "variants". In the absence of a particular testable function and some structural basis for that function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based

approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Further, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In view of this unpredictability, the skilled artisan would not reasonably expect a generically recited polypeptide having at lease 80% identity SEQ ID NO:2 to share the same function as the polypeptide of SEQ ID NO:6, and there is insufficient guidance to direct the skilled artisan as to those essential sequences. Thus the recitation of percent identity language does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

"Fragments."

The instant claim language encompasses fragments of SEQ ID NO:6 of at least 6 contiguous amino acids.

However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:6 would share the activity of SEQ ID NO:6. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled

artisan to determine which subsequences of SEQ ID NO:6 would have the function of the full length molecule.

Further, the term "comprising" in claim 1(b) is open ended and extends the nucleic acid molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length SEQ ID NO:6, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various fragments encompassed by the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. Without detailed direction as to which nucleic acid sequences are essential to the function of the encoded polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of polypeptide sequences encompassed by the instant claims would share the function of SEQ ID NO:6.

"Derivatives" and "analogs."

The instant claim language encompasses derivatives and analogs of SEQ ID NO:6. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Also, as noted supra, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). These references demonstrate that even a single amino acid substitution or what

appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Furthermore, the specification fails to teach what modifications of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

Thus the disclosure of a range of possible protein sequence modifications, in the absence of guidance as to the specific nature of modifications resulting in a functional polypeptide, does not allow the skilled artisan to make and use the nucleic acids encoding the variant polypeptides commensurate in scope with the instant claims without undue experimentation.

"Allelic variants," "homologs," and "hybridization."

Applicant has not provided sufficient biochemical or structural information (e.g. amino acid sequences, etc.) that distinctly identifies the allelic variants or homologs of SEQ ID NO:6, other than the polypeptide SEQ ID NO:6 itself. It is not sufficient to define a specificity by its principal biological activity or structure, e.g. for allelic variants or homologs of SEQ ID NO:6, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

Similarly, the fact that two nucleic acid sequences will hybridize under stringent conditions does not in and of itself require that the two sequences share any functional activity. The instant specification discloses that sequences hybridizing under stringent conditions are at least 60% homologous to each other (page 14 lines 24 – 26). Thus the same observations apply to the recitation of "a nucleic acid that hybridizes under stringent conditions" as were noted above with respect to "percent identity" language.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed polypeptide in manner reasonably correlated with the scope of the claims broadly including any number of allelic variants or homologs of SEQ ID NO:6. The scope of the claims must bear a reasonable correlation with the scope of enablement. The specification does not provide for sufficient enablement for allelic variants or homologs of SEQ ID NO:6 other than that defined by SEQ ID NO:6.

Furthermore, in addition to the lack of sufficient enabling description of the claimed genus of polypeptide variants, Applicant has not provided a sufficient enabling description of an antibody that selectively binds to such variant polypeptides, because such antibody would not reasonably be expected to be reactive with the polypeptide of SEQ ID NO:6, and therefore to be functional in the claimed methods. For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991; see entire document) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody. Further, Li et al. (PNAS 77: 3211-3214, 1980; see entire document) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Therefore, the specification does not provide for sufficient enablement for antibodies reactive with variants or fragments of SEQ ID NO:6 other than those reactive with the polypeptide of SEQ ID NO:6.

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Limiting the scope of the claims to a method utilizing antibodies to the polypeptide of SEQ ID NO:6 would obviate this rejection. It is noted that such amendment would not obviate the rejection set forth in section 13 supra.

15. Claims 17 and 26 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following *Written Description* rejection is set forth herein.

Applicant is not in possession of a method of treating or preventing an immune response-associated disorder (or a pathological state) by administering an antibody that selectively binds to:

(a) a polypeptide comprising an amino acid sequence of SEQ ID NO:6;

(b) a fragment of a polypeptide comprising an amino acid sequence of SEQ ID NO:6, wherein the fragment comprises at least 6 contiguous amino acids of SEQ ID NO:6;

(c) a derivative of a polypeptide comprising an amino acid sequence of SEQ ID NO:6;

(d) an analog of a polypeptide comprising an amino acid sequence of SEQ ID NO:6;

(e) a homolog of a polypeptide comprising an amino acid sequence of SEQ ID NO:6; or

(f) a naturally occurring allelic variant of a polypeptide comprising an amino acid sequence of SEQ ID NO:6, wherein the polypeptide is encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule of SEQ ID NO:6 under stringent conditions.

Again, it is noted that method claims 17 and 26 encompass all the limitations of base claims 10 and 12.

The instant claims do not provide sufficient structural and functional characteristics of the genus of polypeptides encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure. Consequently, the specification does not describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a single polypeptide of SEQ ID NO:6, and polypeptides of SEQ ID NOS: 2 and 4 which differ in the number of Ig-like domains. The instant claims encompass in their breadth *any* polypeptide at lease 80% identical to *any* fragment, derivative, analog, homolog, or allelic variant of the sequence. However, there is insufficient written description of the claimed genus of polypeptides in the absence of defining the relevant identifying characteristics such as the structure or other physical and/or chemical characteristics of the claimed genus.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings,

or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Regarding the instant claim limitations, the specification does not appear to provide an adequate written description for the following reasons:

"Percent identity."

The claims recite a genus of polypeptides having at least 80% identity to a reference sequence, but do not require that the encoded polypeptides share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed three BLAA polypeptides, and thus has disclosed only three "variants". In the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental

research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Thus the recitation of percent identity language, in the absence of *a testable function*, does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

"Fragments."

The instant claim language encompasses fragments of SEQ ID NO:6 of at least 6 contiguous amino acids. However, the specification does not appear to have provided sufficient written description as to which subsequences of SEQ ID NO:6 would share the activity of SEQ ID NO:6. Neither does the specification appear to have provided sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics.

Further, the term "comprising" in claim 1(b) is open ended and extends the nucleic acid molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length SEQ ID NO:6, there does not appear to be sufficient written description in the specification as filed to convey to the skilled artisan that the inventors, at the time the application was filed, had possession of the claimed invention.

"Derivatives" and "analogs."

The instant claim language encompasses derivatives and analogs of SEQ ID NO:6. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol.

8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Also, as noted supra, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Furthermore, the specification fails to provide a sufficient written description as to which modifications of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

Thus the disclosure of a range of possible protein sequence modifications, in the absence of written description of the specific nature of modifications resulting in a functional polypeptide, does not convey to the skilled artisan that the inventors, at the time the application was filed, had possession of the claimed invention.

"Allelic variants," "homologs," and "hybridization."

Applicant has not provided sufficient biochemical or structural information (e.g. amino acid sequences, etc.) that distinctly identifies the allelic variants or homologs of SEQ ID NO:6, other than the polypeptide SEQ ID NO:6 itself. It is not sufficient to define a genus without sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics.

Similarly, the fact that two nucleic acid sequences will hybridize under stringent conditions does not in and of itself require that the two sequences share any functional activity. The instant specification discloses that sequences hybridizing under stringent conditions are at least 60% homologous to each other (page 14 lines 24 – 26). Thus the same observations apply to the recitation of "a nucleic acid that hybridizes under stringent conditions" as were noted above with respect to "percent identity" language.

Furthermore, in addition to the lack of sufficient written description of the claimed genus of polypeptide variants, Applicant has not provided a sufficient written description of an antibody that selectively binds to such variant polypeptides, because such antibody would not reasonably be expected to be reactive with the polypeptide of SEQ ID NO:6, and therefore to be functional in the claimed methods. For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991; see entire document) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody. Further, Li et al. (PNAS 77: 3211-3214, 1980; see entire document) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Therefore, the specification does not provide for sufficient written description to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of antibodies reactive with variants or fragments of SEQ ID NO:6, other than the antibodies reactive with the polypeptide of SEQ ID NO:6.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Limiting the scope of the claims to a method utilizing antibodies to the polypeptide of SEQ ID NO:6 would obviate this rejection. It is noted that such amendment would not obviate the rejection set forth in section 13 supra.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 17 and 26 are rejected under **35 U.S.C. 102(e)** as being anticipated by Mikesell et al. (US Pat. Pub. No. 2002/0095024; see entire document).

Mikesell et al. teach a polypeptide, BSL2 (SEQ ID NO:7), which is 100% identical to the instantly claimed SEQ ID NO:6, as evidenced by the attached alignment. Mikesell et al. further teach methods of immunomodulation in human or animal subjects by administering compositions comprising antibodies to BSL2, e.g. to provide immunosuppression, induce tolerance, or in the treatment of autoimmune diseases (see entire document, in particular, e.g. paragraph 0022).

Therefore the reference teachings anticipate the instant claimed invention.

18. Conclusion: no claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644

August 9, 2005

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
8/11/05

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: June 21, 2005, 08:26:13 ; Search time 160 Seconds
(without alignments)
1281.532 Million cell updates/sec

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Perfect score: 2772
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Gapop 10.0 , Gapext 0.5

Searched: 1714042 seqs, 383979560 residues

Total number of hits satisfying chosen parameters: 1714042

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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2	2772	100.0	534	14	US-10-077-023-7	Sequence 7, Appli
3	2772	100.0	534	15	US-10-380-040A-1	Sequence 1, Appli
4	2772	100.0	534	16	US-10-403-142-140	Sequence 140, App
5	2772	100.0	534	16	US-10-484-122-2	Sequence 2, Appli
6	2772	100.0	534	17	US-10-824-481-6	Sequence 6, Appli
7	2613	94.3	606	16	US-10-403-142-134	Sequence 134, App
8	2583.5	93.2	522	16	US-10-403-142-132	Sequence 132, App
9	2582.5	93.2	522	16	US-10-403-142-150	Sequence 150, App
10	2579.5	93.1	522	16	US-10-403-142-146	Sequence 146, App
11	2579.5	93.1	522	16	US-10-403-142-148	Sequence 148, App
12	2579.5	93.1	522	16	US-10-403-142-154	Sequence 154, App
13	2575.5	92.9	522	16	US-10-403-142-156	Sequence 156, App
14	2414	87.1	698	9	US-09-875-338-9	Sequence 9, Appli
15	2414	87.1	698	14	US-10-077-023-9	Sequence 9, Appli
16	2414	87.1	717	16	US-10-484-122-4	Sequence 4, Appli
17	2271	81.9	700	17	US-10-824-481-11	Sequence 11, Appl
18	2244	81.0	435	16	US-10-403-142-144	Sequence 144, App
19	1954	70.5	387	9	US-09-789-561-156	Sequence 156, App
20	1954	70.5	387	17	US-10-883-936-156	Sequence 156, App
21	1843.5	66.5	453	16	US-10-403-142-136	Sequence 136, App
22	1529	55.2	316	9	US-09-910-174A-24	Sequence 24, Appl
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40	1522	54.9	316	9	US-09-978-295A-137	Sequence 137, App
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42	1522	54.9	316	9	US-09-978-697-137	Sequence 137, App
43	1522	54.9	316	9	US-09-978-192A-137	Sequence 137, App
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ALIGNMENTS

RESULT 1
US-09-875-338-7
; Sequence 7, Application US/09875338
; Patent No. US20020095024A1
; GENERAL INFORMATION:
; APPLICANT: MIKESELL, GLEN E.
; APPLICANT: CHANG, HAN
; APPLICANT: FINGER, JOSHUA N.
; APPLICANT: YANG, GUCHEN
; APPLICANT: LU, PIN
; APPLICANT: ZHOU, XIA-DI
; APPLICANT: PEACH, ROBERT
; TITLE OF INVENTION: B7-RELATED NUCLEIC ACIDS AND POLYPEPTIDES USEFUL FOR
; TITLE OF INVENTION: IMMUNOMODULATION
; FILE REFERENCE: 3053-4071US2
; CURRENT APPLICATION NUMBER: US/09/875,338
; CURRENT FILING DATE: 2001-06-06
; PRIOR APPLICATION NUMBER: 60/272,107
; PRIOR FILING DATE: 2001-02-28
; PRIOR APPLICATION NUMBER: 60/209,811
; PRIOR FILING DATE: 2000-06-06
; NUMBER OF SEQ ID NOS: 94
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 7
; LENGTH: 534
; TYPE: PRT
; ORGANISM: Homo sapiens
US-09-875-338-7

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Best Local Similarity 100.0%; Pred. No. 3.5e-192;
Matches 534; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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; Sequence 7, Application US/10077023
; Publication No. US20030031675A1
; GENERAL INFORMATION:
; APPLICANT: MIKESELL, GLEN E.
; APPLICANT: CHANG, HAN
; APPLICANT: FINGER, JOSHUA N.
; APPLICANT: YANG, GUCHEN
; APPLICANT: LU, PIN
; APPLICANT: ZHOU, XIA-DI
; APPLICANT: PEACH, ROBERT
; TITLE OF INVENTION: B7-RELATED NUCLEIC ACIDS AND POLYPEPTIDES USEFUL FOR
; TITLE OF INVENTION: IMMUNOMODULATION
; FILE REFERENCE: 3053-4071US3
; CURRENT APPLICATION NUMBER: US/10/077,023
; CURRENT FILING DATE: 2002-02-15
; PRIOR APPLICATION NUMBER: 60/272,107
; PRIOR FILING DATE: 2001-02-28
; PRIOR APPLICATION NUMBER: 60/209,811
; PRIOR FILING DATE: 2000-06-06
; NUMBER OF SEQ ID NOS: 138
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 7
; LENGTH: 534
; TYPE: PRT
; ORGANISM: Homo sapiens
US-10-077-023-7

Query Match 100.0%; Score 2772; DB 14; Length 534;
Best Local Similarity 100.0%; Pred. No. 3.5e-192;
Matches 534; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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; Sequence 1, Application US/10380040A
; Publication No. US20040077043A1
; GENERAL INFORMATION:
; APPLICANT: Kirin Beer Kabushiki Kaisha
; TITLE OF INVENTION: A NOVEL DENDRITIC CELL MEMBRANE MOLECULE AND USE THEREOF
; FILE REFERENCE: PH-1297PCT-US
; CURRENT APPLICATION NUMBER: US/10/380,040A
; CURRENT FILING DATE: 2003-03-11
; PRIOR APPLICATION NUMBER: JP 2000-277352
; PRIOR FILING DATE: 2000-09-12
; NUMBER OF SEQ ID NOS: 8
; SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 1
; LENGTH: 534
; TYPE: PRT
; ORGANISM: Homo sapiens
US-10-380-040A-1

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Best Local Similarity 100.0%; Pred. No. 3.5e-192;
Matches 534; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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